REMARKS

Claims 1-19, 21, 31, 32, 41-43, 52, 53 and 57-61 were pending in the subject application. By this Amendment, applicants have cancelled claims 1-11 and 14 without prejudice to or disclaimer of their right to the subject matter, amended claims 12, 16, 19, 21, 32, 43 and 57, and have added new claims 62-65. Accordingly, claims 12, 13, 15-19, 21, 31, 32, 41-43, 52-53, and 57-65 are pending.

Support for the amendment to claim 12 may be found, *inter alia*, on page 12, lines 13-34, and on page 26, lines 19-32 of the subject application.

Support for the amendment to claim 57 may be found, *inter alia*, on page 4, lines 15-27, and on page 12, lines 14-22, of the subject application.

Support for new claim 62 may be found, *inter alia*, on page 23, line 27 of the subject application.

Support for new claim 63 may be found, *inter alia*, on page 22, line 10 of the subject application.

Support for new claim 64 may be found, *inter alia*, on page 32, line 29 of the subject application.

Support for new claim 65 may be found, *inter alia*, on page 26, lines 19-32 of the subject application.

Applicants' response to the maintained obviousness rejections

Applicants respectfully submit that the claims now pending in the subject application are not subject to the rejections set forth in the September 22, 2006 Final Office Action.

On pages 3-4, in Sections 5-8 of the September 22, 2006 Final Office Action, the Examiner has maintained the rejections of the claims under 35 U.S.C. §103. Specifically, the Examiner maintained the rejections as follows:

In Section 5:

-claims 1-4, 7, 8, 11, 19, 21 and 31 under 35 U.S.C. §103(a) as unpatentable over U.S. Patent Application Publication No. 2004/0127408 A1 to Mozes ("Mozes") in view of U.S. Patent No. 5,997,856 to Hora et al. ("the '856 patent" or "Hora");

In Section 6:

-claims 5 and 6 under 35 U.S.C. §103 over Mozes in view of the '856 patent as applied to claims 1-4, 7, 8, 11, 31, 42, 53, 57 and 59-61 and in further view of Anderson, B.D. and Flora, K.P. (Chapter 34, pages 739-754, *The Practice of Medicinal Chemistry*, edited by Camilles Georges Wermuth, Academic Press 1996); and

In Section 7:

-claims 9, 10 and 12-18 under 35 U.S.C. §103 over Mozes in view of the '856 patent as applied to claims 1-4, 7, 8, 11 and 31 and further in view of U.S. Patent No. 5,134,127 to Stella et al. ("the '127 patent" or "Stella").

Applicants' Reply

Rejections of Section 5 and 6:

In response, Applicants submit that the rejections of Sections 5 and 6 of the September 22, 2006 Final Office Action are moot due to the cancellation of claims in this Amendment. Furthermore, any rejection in Section 5 and 6 applicable to claims not cancelled by this Amendment is moot due to the amendments made herein to the dependencies of such claims.

Rejections of Section 7 (Mozes/Hora/Stella)

Applicants respectfully submit that the obviousness rejection maintained in Section 7 of the September 22, 2006 Final Office Action fails to satisfy at least the following elements of the legal standard of an obviousness rejection:

1. THE PRIOR ART DOES NOT TEACH ALL ELEMENTS OF THE CLAIMS.

In response, Applicants respectfully maintain that a) the combination of Mozes, the '856 patent and the '127 patent, does not teach all claim elements; and b) the combination is improper.

Mozes (U.S. 2004/0127408A1) fails to teach any cyclodextrin as a solubility enhancer, and specifically fails to teach the hepta-(sulfobutyl ether)-β-cyclodextrin as a solubility enhancer. Hora, like Mozes, also fails to teach a hepta-(sulfobutyl ether)-β-cyclodextrin as a solubility enhancer. The disclosure of Stella is not applicable to peptides.

The disclosure of Stella teaches cyclodextrins as solubility enhancers for small molecules such as digoxin and progesterone. Stella does not teach cyclodextrins as solubility enhancers for peptides. In addition, the teachings of Stella show that the solubility enhancement with cyclodextrins is unpredictable even for small molecules such as digoxin and progesterone. Most importantly, Hora (column 19, lines 38-58) teaches that solubilization and stabilization of peptides is difficult to accomplish and that achieving "solubilization/stabilization ... without appreciable loss of activity, cannot be readily predicted". (Emphasis added.) In order to establish a *prima facie* case of obviousness, it must be shown through explicit analysis that the claimed invention is no more than the "predictable use" of the prior art. *KSR v. Teleflex*, 550 U.S. _____ (2007). As shown by Hora, one of skill in the art was well aware that success in solubilizing/stabilizing a peptide cannot be readily predicted.

Hora teaches that polypeptides present unique solubility problems as compared to other drug molecules, as a result of their unique structure. In addition, Hora provides what it deems to be a select group of cyclodextrins that are well-suited for use as solubilizing/stabilizing peptides; this select group includes the hydroxypropyl, hydroxymethyl, glucosyl, maltosyl and maltotriosyl derivatives of β- and γ-cyclodextrin. Importantly hepta-(sulfobutyl ether)-β-cyclodextrin is not in this select group nor is any sulfobutyl substituted β-cyclodextrin. Clearly, Hora teaches away from using hepta-(sulfobutyl ether)-β-cyclodextrin by stating that a different group has been determined to be "a selected group

of cyclodextrins ... well-suited for ... polypeptides ... ". Clearly, one of skill in the art cannot have a reasonable expectation of success of solubilizing peptides while maintaining activity with cyclodextrins other than those described by Hora. It is well settled that "when the prior art teaches away" from the claimed invention, the claimed invention is not obvious. See, e.g. *KSR v. Teleflex*, 550 U.S. _____(2007), citing *U.S. v. Adams*, 383 U.S. 39, 40 (1996). Finally, Stella is not properly combined (see M.P.E.P. §2143.01), with Mozes and Hora because Stella is not relevant to peptides.

2. LACK OF A PRIOR ART PROCESS FOR MAKING THE CLAIMED PRODUCT SUPPORTS A FINDING OF NON-OBVIOUSNESS.

Furthermore, the prior art fails to disclose a method for making the claimed pharmaceutical composition. Example 2 of the subject application describes applicants' method for preparing a solution of compound 1 with Capsitol® (sodium salt of hepta-(sulfobutyl ether)-β-cyclodextrin). Applicants specifically refer the Examiner to page 32, lines 15-30 of the subject application. The applicants' method for solubilizing compound 1 with Capsitol® specifically relies on steps 5 and 6 which involve cycling of the pH of the solution. It is imperative that the pH cycling is performed in order to achieve peptide solubilization. In step 5, the pH of the peptide/Capsitol® solution is raised, and then in step 6, the pH is corrected to the range of pH 7.5 to 8.5. As noted on lines 15-30 of page 32 of the specification, the claimed composition was <u>not achieved without the pH cycling steps</u>.

The prior art, for example Hora, does not teach that these pH cycling steps or suggest that they are necessary. The method of Hora merely involves combination of hydroxypropyl-β-cyclodextrin(HPBCD), the peptide (IL-2), sucrose and citrate buffer, followed by lyophilization and addition of water. Hora does not cycle the pH in order to achieve solubility.

In addition, applicants' method allows solubility of a significantly higher concentration of peptide than the method of Hora. Hora, as shown in column 22, table 2, achieves formulations of no more than 1.0 mg/ml peptide. However, applicants achieve formulations at a concentration of 2.5 mg/ml peptide (see, examples and claims 15 and 18 of the subject application).

According to M.P.E.P. §2144.09 "[I]f the prior art of record fails to disclose or render obvious a method for making a claimed compound, at the time the invention was made, it may not be legally concluded that the compound itself is in the possession of the public. In this context, we say that the absence of a known or obvious process for making the claimed compounds overcomes a presumption that the compounds are obvious, based on the close relationships between their structures and those of prior art compounds." *In re Hoeksema*, 399 F.2d 269, 274-75, 158 USPQ 597, 601 (CCPA 1968). Accordingly, since the prior art fails to teach or suggest a method of making the claimed pharmaceutical composition, the claimed composition cannot be obvious over the prior art.

3. THE PRIOR ART FAILS TO TEACH SELECTION OF CYCLODEXTRINS FROM AMONG THE MULTITUDE OF SOLUBILITY ENHANCERS.

Cyclodextrins are not a common class of solubility enhancers. Cyclodextrins have known problems, as explained on pages 14-15 of Applicants' July 27, 2006 Amendment. The September 22, 2006 Final Office Action did not dispute this.

The primary reference, Mozes, does not indicate there is a need for any solubility enhancer, and certainly does not suggest a need for cyclodextrins. If anything, Mozes teaches in its paragraph [0088] that solubility and stability can be modified by making "derivatives and salts" of the peptide. A cyclodextrin as claimed by Applicants is neither "derivatives" nor "salts".

Therefore, the art fails to teach or suggest to one skilled in the art the selection of cyclodextrins for use with the recited peptide.

4. THE PRIOR ART FAILS TO PROVIDE AN EXPECTATION THAT THE COMBINATION OF CYCLODEXTRIN WITH THE SPECIFIC RECITED PEPTIDE WOULD IMPROVE SOLUBILITY OF THE RECITED PEPTIDE.

Whether any given solubility enhancer would be effective for a given peptide class cannot be predicted. See, e.g. Hora, column 19, lines 38-51. See, also, applicants' examples showing that applicants needed to test over 40 solubility enhancers to find several that could improve the solubility of the recited peptide, only to then find some to result in non-active compositions, and finally surprisingly finding only the β-cyclodextrin to both improve solubility and maintain

biological activity. See, pages 23-31 of the subject application.

Therefore, one of skill would not expect that the solubility of the recited peptide would be improved by cyclodextrins.

5. THE PRIOR ART FAILS TO PROVIDE AN EXPECTATION THAT THE COMBINATION OF CYCLODEXTRIN WITH THE SPECIFIC RECITED PEPTIDE WOULD RESULT IN A BIOLOGICALLY ACTIVE PHARMACEUTICAL COMPOSITION.

Even if a solubility enhancer improves the solubility of a peptide, one of skill would not expect the resulting composition to necessarily be biologically active. The September 22, 2006 Final Office Action did not dispute this.

See, for example, Applicants' results with PEG 400, which improved solubility but eliminated biological activity of the recited peptide (page 25, lines 8-12 of the subject application). See, also, Table 3 of Hora showing that 2 of the three formulations with cyclodextrin had significantly reduced bioactivity (36% and 45% less!), and a fourth one with insulin that *was not even shown*.

Clearly, therefore, the prior art did not provide the expectation of success necessary for a proper obviousness rejection.

Applicants note the September 22, 2006 Final Office Action relies on Stella et al. to assert that cyclodextrins "reduced toxicity, and reduced membrane disruption …." However, Stella et al. do not teach that a cyclodextrin always maintains bioactivity of the compound. More importantly, Stella et al.

deal with small molecule drugs, and clearly cannot offer any teaching relevant to peptides, much less relevant to the claimed peptide.

6. THE DEPENDENT CLAIMS RECITE ADDITIONAL UNOBVIOUS FEATURES.

The following claims recite additional unobvious features:

Claim 16

The cited prior art contains no teaching that 120 mg/ml is preferred or that such a concentration imparts solubility at a pH of 7.5-8.5. Hora only achieves solubility at pH 6.5.

Claim 17

Solubilization of a peptide at a concentration of 1.0 mg/ml at a pH of 7.5-8.5 is not reported in the cited prior art. The formulations of Hora, as shown at column 22, table 2, show formulations that have a pH of 6.5.

Claim 18

No cited reference shows such a solubility level (2.5 mg/ml) or provides an expectation that such a level is possible with hepta-(sulfobutyl ether)-β-cyclodextrin. Clearly, therefore, one skilled in the art could not have a reasonable expectation of successfully solubilizing the specific peptide (SEQ ID NO. 1) to a concentration of 2.5 mg/ml while maintaining biological activity.

Claim 19

Applicants have shown *in vivo* activity of the pharmaceutical composition (see pages 36-38), whereas the prior art fails to predict that *in vivo* activity of the peptide would be maintained once formulated with a solubility enhancer. (See, e.g. applicants' results with PEG 400 described on page 25, lines 8-12 of this application.)

Claim 62

The prior art does not teach or suggest how to achieve an iso-osmotic composition. The preferred claimed amount of hepta-(sulfobutyl ether)-β-cyclodextrin in solution is 12% (120 mg/ml). Applicants found that hepta-(sulfobutyl ether)-β-cyclodextrin is most effective in enhancing solubility of peptides at around such a level. Using more than 12% hepta-(sulfobutyl ether)-β-cyclodextrin does not enhance solubility, but negatively affects osmolarity. The cited prior art fails to teach or suggest the osmolarity problem. For example, table 3 on page 31 of the subject application which points out that the standard amount of hepta-(sulfobutyl ether)-β-cyclodextrin is up to 30%.

Claim 63

The prior art does not suggest using hepta-(sulfobutyl ether)-β-cyclodextrin in a subcutaneous injection, which has certain requirements. A subcutaneous injection requires a pH between 4-9, more preferably a neutral pH, an iso-osmotic solution, and an injection volume not more than 1 mL. Drugs which are currently on the market using hepta-(sulfobutyl ether)-β-cyclodextrin as excipient are administered either

intravenously(IV) or intramuscularly(IM), such as Vfend® and Zeldox®/Geodon®. There is no volume limitation for IV, and IM products can be administered in up to 3 mL of volume. In contrast, subcutaneous injections are limited in volume to only 1 mL. Therefore, it is critical for these drugs to be sufficiently soluble so that the desired concentration can be administered in 1 mL.

Further, it is important to note that there are no approved marketed products for subcutaneous use which contain hepta-(sulfobutyl ether)-β-cyclodextrin. There are IV and IM products, but not subcutaneous. The other marketed products which contain Capsitol® are not peptide-based, rather, they are insoluble small molecules. Moreover, Stella teaches away from the use of cyclodextrins for subcutaneous injections. Stella (see column 2, lines 45-53) states that "despite this pharmaceutical utility, cyclodextrins are not without their limitations. The use of cyclodextrins in the clinical setting is limited to oral and topical dosage forms as the cyclodextrins exhibit nephrotoxicity upon entering the body unmetabolized. Since mammalian enzymes are specific for the degradation of linear starch molecules, the cyclodextrins remain largely unmetabolized and accumulate, due to their recirculation and readsorption, in the proximal tubule cells." Therefore, there is nothing in the prior art that would teach, suggest, or motivate one of skill in the art to utilize cyclodextrins in a subcutaneous injection, and certainly nothing in the prior art providing an expectation of success of cyclodextrins in a subcutaneous injection.

Claim 64

The prior art does not suggest using HCl or NaOH with hepta-(sulfobutyl ether)-β-cyclodextrin.

Conclusion

In conclusion, Applicants respectfully submit that the claimed invention is inventive over the prior art. Applicants also maintain that the obviousness rejections of record are fundamentally deficient for any one of the six reasons discussed above. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections.

Request for Examiner Interview

Applicants hereby request the opportunity to discuss the subject application with the Examiner after the Examiner considers this Amendment. Applicants respectfully request the Examiner to contact the undersigned at the telephone number provided below to schedule the interview.

No fee, other than the enclosed $790.00 fee for the RCE and the enclosed $1590.00 fee for a four-month extension, is deemed necessary in connection with the filing of this Amendment and RCE Submission. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Gary J. Gershik

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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